Neurology

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Learning Objectives:

1. Differentiate between various antiepileptic drugs based on use and adverse effects.
2. Develop a treatment strategy for status epilepticus.
3. Identify appropriate treatment strategies for primary and secondary stroke prevention.
4. Determine appropriateness of treatment with tissue plasminogen activator for acute stroke treatment.
5. Examine common adverse effects associated with treatment of Parkinson disease.
6. Differentiate between regimens for acute and prophylactic treatment of migraine, tension, and cluster headaches.

Self-Assessment Questions:

Answers to these questions may be found at the end of this chapter.

1. T.L. is a 35-year-old man with complex partial seizures. He is otherwise healthy. He was placed on phenytoin after a seizure about 2 months ago. He is currently taking phenytoin 100 mg three capsules orally every night. During his clinic visit, he tells you that he has had no seizures, and he has no signs of toxicity. He is allergic to sulfa drugs. His phenytoin serum concentration is 17.7 mcg/mL. How would you interpret this concentration?
   A. It is too low.
   B. It is too high.
   C. It is just right.
   D. He should have an albumin determination to interpret this concentration.

2. When T.L. (from Question No. 1) returns for his appointment with you, he tells you that his dentist told him 3 months ago that he had gingival hyperplasia. He began an intensive oral hygiene regimen and returned to see the dentist last week. Unfortunately, there has been no improvement and he was told that he will require gum reduction surgery if it does not improve. T.L. wants to discontinue the phenytoin. As you consider drugs to replace the phenytoin, which one of the following is contraindicated for T.L.?
   A. Oxcarbazepine.
   B. Valproic acid.
   C. Zonisamide.
   D. Tiagabine.

3. B.V. is a 28-year-old woman brought to your emergency department for treatment of status epilepticus. She is given lorazepam 4 mg intravenously with subsequent seizure cessation. Which one of the following medications should be the next treatment step for B.V.?
   A. Topiramate.
   B. Phenobarbital.
   C. Zonisamide.
   D. Diazepam.

4. J.H. is a 42-year-old man with complex partial seizures for which he was prescribed topiramate. He has been increasing the dose of topiramate every other day per instructions from his primary care provider. He comes into the pharmacy where you work, but seems a little confused and has difficulty finding the words to have a conversation with you. Which one of the following is the best assessment of J.H.'s condition?
   A. Stop his topiramate; he is having an allergic reaction.
   B. Increase his topiramate dose; he is having partial seizures.
   C. Slow down the rate of topiramate titration; he is having psychomotor slowing.
   D. Get a topiramate serum concentration; he is likely supratherapeutic.

5. R.H. is a 59-year-old man who presents to the emergency department for new-onset left-sided weakness that began 3.5 hours ago. He has a history of hypertension and coronary artery disease. His medication list includes atenolol 50 mg/day orally, hydrochlorothiazide 25 mg/day orally, and aspirin 325 mg/day orally. His vital signs are blood pressure 160/92 mm Hg, pulse 92 beats/minute, respiration rate 14 breaths/minute, and temperature 38°C. The treatment team is evaluating this patient for treatment with tissue plasminogen activator and is asking your opinion. Which one of the following should be your reply based on this information?
   A. R.H. should be treated with tissue plasminogen activator.
   B. R.H. should not be treated with tissue plasminogen activator because onset of his stroke symptoms was 3.5 hours ago.
   C. R.H. should not be treated with tissue plasminogen activator because he has hypertension.

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D. R.H. should not be treated with tissue plasminogen activator because he is taking aspirin.

6. R.H. (from Question No. 5) survives his stroke. As part of his discharge treatment plan, you evaluate his risk factors for a second stroke. Which one of the following medications for secondary stroke prevention do you recommend to begin with?
   A. Aspirin.
   B. Enoxaparin.
   C. Heparin.
   D. Clopidogrel.

7. C.P. is a 69-year-old man diagnosed with Parkinson disease 7 years ago. He states that he is most bothered by his bradykinesia symptoms. On examination, he also has a pronounced tremor, postural instability, and masked facial expression. He currently takes carbidopa/levodopa 25 mg/100 mg orally 4 times/day, pergolide 0.25 mg orally 3 times/day, selegiline 5 mg orally 2 times/day, and entacapone 200 mg orally 4 times/day. He has no medication allergies. He also describes a worsening of his Parkinson disease symptoms that fluctuate during the day. He finds that his symptoms return randomly during the day. He has developed a charting system for his symptoms during the day, and there seems to be no relationship with the time he is scheduled to take his doses of carbidopa/levodopa. Which one of the following conditions best describes C.P.'s fluctuating Parkinson disease symptoms?
   A. Wearing off.
   B. On-off.
   C. Dyskinesia.
   D. Dystonia.

8. Which of C.P.'s (from Question No. 7) medications has been associated with valvular heart disease?
   A. Carbidopa/levodopa.
   B. Pergolide.
   C. Selegiline.
   D. Entacapone.

9. For his symptoms, C.P. (from Question No. 7) is given a prescription for apomorphine. Which one of the following is a true statement regarding this medication?
   A. He must be trained on self-injection technique with saline, but he can administer his first dose of apomorphine at home when he needs it.
   B. He should not take apomorphine if he is allergic to penicillin.
   C. If he does not take a dose for more than a week, he should begin with a loading dose with his next injection.
   D. It may cause severe nausea and vomiting.

10. W.S. is a 57-year-old man who is started on rasagiline for treatment of his newly diagnosed Parkinson disease. He develops a cough, body aches, and nasal congestion. Which one of the following drugs could be safely recommended for W.S.?
   A. Guaifenesin.
   B. Dextromethorphan.
   C. Tramadol.
   D. Pseudoephedrine.

11. R.M. is a 47-year-old woman with long-standing migraine headaches. The headache pain is easily relieved with sumatriptan 100 mg orally as occasion requires. However, with her last dose, she experienced substernal chest pain radiating to her left arm. She reported to her local emergency department and had a complete work-up. Her final diagnosis was coronary artery disease and hypertension. For these conditions, she was placed on hydrochlorothiazide 25 mg orally every morning. R.M.'s family physician asks you which one of the following drugs R.M. should use for her migraine headaches.
   A. Frovatriptan.
   B. Zolmitriptan.
   C. Dihydroergotamine.
   D. Naproxen.

12. If R.M. (from Question 11) requires a medication for migraine prophylaxis, which one of the following would you recommend?
   A. Propranolol.
   B. Valproic acid.
   C. Amitriptyline.
   D. Gabapentin.

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I. EPILEPSY

A. Epidemiology
1. Ten percent of the population will have a seizure.
2. About 50 million people worldwide have epilepsy.
3. About 70% of patients can become seizure free with appropriate management.

B. Classification of Seizure Types
Seizures are generally classified according to the International League Against Epilepsy (ILAE) scheme adopted in 1981. There is a proposal currently to alter this scheme somewhat. (A complete discussion of this change can be found in Engle J. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. Epilepsia 2001;42:796–803. It is available on the Internet at *http://ilae.org/pubs/JUNE2001.pdf*. Accessed August 25, 2007. A summary of the classification scheme can be found at *http://www.ilae-epilepsy.org/Visitors/Centre/ctf/seizure_types.cfm.* Accessed August 25, 2007)
1. Partial Seizures (proposed name change to Focal Seizures) begin in one hemisphere of the brain.
   a. Simple (proposal to eliminate distinction between simple and complex partial seizures): No loss of consciousness throughout seizure. Symptoms may be classified as motor (involving any part of the body), autonomic (e.g., pallor, flushing, vomiting, sweating, vertigo, tachycardia), or sensory (e.g., visual, auditory, olfactory, gustatory sensations).
   b. Complex: loss of consciousness. Complex partial seizures may be preceded by a prodrome and begin with an aura. A prodrome is an awareness of an impending seizure before it occurs. The prodrome may consist of headache, insomnia, irritability, or feeling of impending doom. The aura that accompanies a complex partial seizures may be a simple partial seizure consisting of sensory or autonomic symptoms. Patients may experience feelings of fear, embarrassment, or déjà vu. Automatic behavior (automatism) and psychic symptoms may occur. Automatisms may include lip smacking, chewing, swallowing, abnormal tongue movements, scratching, thrashing of the arms or legs, fumbling with clothing, or snapping the fingers. Psychic symptoms include illusions, hallucinations, emotional changes, dysphasia, and cognitive problems. Complex partial seizures usually are short in duration (seconds to minutes).
   c. Secondarily generalized: begins as a partial seizure but spreads to involve both hemispheres of the brain.
2. Generalized seizures begin in both hemispheres of the brain.
   a. Absence: Typical absence seizures are brief and abrupt, last 10–30 seconds, and occur in clusters. Absence seizures usually result in a short loss of consciousness, or the patient may be observed to stare, be motionless, or have a distant expression on his/her face. Electroencephalograms performed during seizure activity usually show three Hz spike-and-wave complexes.
   b. Myoclonic: Consist of brief, lightning-like jerking movements of the whole body or the upper and occasionally lower extremities.
   c. Tonic-clonic: Typically, there are five phases of a primary tonic-clonic seizure: flexion, extension, tremor, clonic, and postictal. During the flexion phase, the patient's mouth may be held partially open, and the patient may experience upward eye movement, involvement of the extremities, and loss of consciousness. In the extension phase, a patient may be noted to extend his or her back and neck; experience contraction of thoracic and abdominal muscles; be apneic; and have flexion, extension, and adduction of the extremities. The patient may cry out as air is forced from the lungs in this phase. The tremor phase occurs as the patient goes from tonic rigidity to tremors and then to a clonic state. During the clonic phase, the patient will experience rhythmic jerks. After

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the seizure, the patient may be postictal. The length of the entire seizure is usually 1–3 minutes. Before the seizure, a patient may experience a prodrome, but not an aura.

d. Clonic: only the clonic phase of a tonic-clonic seizure; rhythmic, repetitive, jerking muscle movements.
e. Tonic: only the flexion and/or extension phases of a tonic-clonic seizure.
f. Atonic: characterized by a loss of muscle tone. Atonic seizures are often described as drop attacks in which a patient loses tone and falls to the ground.

3. Status epilepticus is a generalized seizure that lasts more than 20 minutes OR recurrent seizures of sufficient frequency that the patient does not regain consciousness between episodes.
4. Pseudoseizures are paroxysmal nonepileptic episodes resembling epileptic seizures that can be organic or psychogenic in origin.

C. Diagnosis
1. Physical examination should be performed with special attention given to neurological findings. The neurologic examination may include examination of the head, vision, cranial nerves, motor function, cerebellar function, and sensory function.
2. Laboratory tests are based on the history and physical examination results; a full diagnostic onslaught is unnecessary in many patients. Because metabolic causes of seizures are common, serum glucose, electrolytes, calcium, and renal function tests may be required.
3. Electroencephalogram is used to help confirm the diagnosis, classify seizures, locate the site of the seizures, and select the best antiepileptic drug. The best time to perform an electroencephalogram is while the patient is having seizures. If it is not possible to perform the electroencephalogram during seizures, the electroencephalogram should be performed as soon after the seizure as possible. Depending on the clinical situation, an electroencephalogram may be obtained under normal conditions, when the patient is sleep deprived, or when the patient is asleep. Some patients whose seizures are difficult to diagnose and/or control may require prolonged closed circuit video–electroencephalogram monitoring. Keep in mind that a inter-ictal (when the patient is not having clinical seizures) electroencephalogram may be normal but does not preclude the diagnosis of epilepsy.
4. Magnetic resonance imaging is the neuroimaging technique of choice for epilepsy. Computed tomography scanning can be useful in finding brain lesions when a magnetic resonance imaging cannot be performed in a timely fashion.

D. Treatment
1. Medications (please see Tables 1–4)
a. Benzodiazepines
i. Mechanism of action: augment gamma-aminobutyric acid–mediated chloride influx.
ii. Tolerance may develop: usually used as adjunctive, short-term therapy.
iii. Most commonly used drugs: clorazepate, clonazepam.
b. Carbamazepine
i. Mechanism of action: sodium channel blocker.
ii. Pharmacokinetics: enzyme inducer, autoinduction.
iii. Adverse effects: rash, syndrome of inappropriate antidiuretic hormone release, aplastic anemia, thrombocytopenia, anemia, leucopenia.
(a) Increased risk of Stevens-Johnson syndrome and toxic epidermal necrosis can be predicted by the presence of HLA-B*1502. This genetic blood test should be performed in patients of Asian ancestry prior to beginning carbamazepine. However, patients who have been taking carbamazepine for long durations without developing skin rash do not require testing.
iv. Extended-release tablets (Tegretol XR) 100 mg, 200 mg, and 400 mg. Extended-release capsules (Carbatrol) 200 and 300 mg available. Do not crush or chew. Ghost

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tablets can be seen in the stool with the extended-release tablets (Tegretol XR).

c. Ethosuximide
   i. Mechanism of action: T-type calcium current blocker
   ii. Useful only for absence seizures

d. Felbamate
   i. Mechanism of action: blocks glycine site on *N*-methyl-D-aspartate receptor
   ii. Serious adverse effects: hepatotoxicity, aplastic anemia. Patient or guardian must sign consent form; used only when seizures are severe and refractory to other medicines and benefit clearly outweighs the potential adverse effects.

Table 1. Medication Selection for Various Seizure Types

Drug	Simple Partial	Complex Partial	Generalized Tonic-Clonic	Absence	Atypical Absence	Atonic	Myoclonic	Infantile Spasms	Status Epilepticus
Acetazolamide	4	4	4	3	3	—	—	—	—
Corticotropin	—	—	—	—	—	—	—	1	—
Carbamazepine	1	1	1	—	—	4	4	—	—
Clonazepam	3	3	3	2	2	1	1	2	—
Diazepam	—	—	—	—	4	—	4	4	1
Ethosuximide	—	—	—	1	1	—	4	—	—
Felbamate	5	5	5	5	—	—	5	—	—
Lorazepam	3	–	3	3	3	–	3	—	1
Gabapentin	2	2	4	—	—	—	—	—	—
Lamotrigine	1	1	2	2	4	3	3	—	—
Levetiracetam	4	4	4	4	—	—	4	—	—
Oxcarbazepine	1	1	2	—	—	3	3	—	—
Phenobarbital	1	1	1	1	—	—	3	—	—
Phenytoin	1	1	1	1	—	—	3	—	—
Prednisone	—	—	—	—	—	—	—	—	1
Pregabalin	4	4	—	—	—	—	—	—	—
Primidone	2	2	2	2	—	—	—	—	—
Tiagabine	4	4	—	—	—	4	4	—	—
Topiramate	1	1	1	3	–	–	3	—	—
Valproic acid	2	2	1	1	1	1	1	1	2
Zonisamide	4	4	—	—	—	—	4	—	—

1 = First-line drug; 2 = second-line drug; 3 = some therapeutic effect; 4 = adjunctive therapy; 5 = used only when benefits outweigh risks.

e. Fosphenytoin
   i. Mechanism of action: prodrug for phenytoin; sodium channel blocker.
   ii. Uses: parenteral formulation for loading or maintenance dosing in place of phenytoin; status epilepticus.
   iii. Pharmacokinetics: enzyme inducer, nonlinear kinetics.
   iv. Dosing: Phenytoin equivalents are used; 1 mg of phenytoin = 1.5 mg of fosphenytoin = 1 mg of phenytoin equivalent. Intramuscular or intravenous dosing is appropriate.
   v. Adverse effects: hypotension, perianal itching.
   vi. Advantages over phenytoin
      (a) Intramuscular or intravenous dosing.
      (b) Phlebitis is minimized.
      (c) Infusion can be up to 150 mg phenytoin equivalents/minute.
      (d) Can deliver in normal saline solution or D_5W (5% dextrose [in water] injection).

f. Gabapentin
   i. Mechanism of action: unknown.
   ii. Pharmacokinetics: not metabolized, eliminated renally; adjustments may be

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necessary for renal dysfunction and hemodialysis.
iii. Also has a Food and Drug Administration (FDA) indication for treatment of postherpetic neuralgia pain.
iv. Doses frequently exceed product information maximum of 3600 mg/day.

Table 2. Selected Interactions Between Antiepileptic Medications

AED*	Added AED	Change in Serum Concentration of the Initial AED	Mechanism
Carbamazepine	Ethosuximide	Decreased	Increased carbamazepine metabolism
	Felbamate	Decreased, increased epoxide	Inhibits epoxide degradation
	Phenytoin	Decreased	Increased carbamazepine metabolism
	Phenobarbital	Decreased	Same as above
	Primidone	Decreased	Same as above
Felbamate	Phenytoin	Decreased	Increased metabolism
	Carbamazepine	Decreased	Increased metabolism
Lamotrigine	Phenytoin	Decreased	Increased metabolism
	Carbamazepine	Decreased	Same as above
	Primidone	Decreased	Same as above
	Phenobarbital	Decreased	Same as above
	Valproic acid	Increased	Decreased metabolism
Oxcarbazepine	Carbamazepine	Decreased	Increased metabolism
	Phenobarbital	Decreased	Same as above
	Phenytoin	Decreased	Same as above
	Valproic acid	Decreased	?
Phenobarbital	Oxcarbazepine	Increased	Competition for hepatic metabolism
	Phenytoin	Increased	Same as above
	Valproic acid	Increased	Same as above
Phenytoin	Carbamazepine	Decreased	Increased metabolism
	Oxcarbazepine	Increased/no change	?
	Phenobarbital	Increased/decreased	Decreased/increased metabolism
	Topiramate	Increased	Decreased metabolism
	Valproic acid	Decreased total; increased free	Displacement from binding sites
Primidone	Carbamazepine	Increased phenobarbital conc.	?
	Phenytoin	Increased phenobarbital conc.	?
Topiramate	Carbamazepine	Decreased	Increased metabolism
	Lamotrigine	Decreased	?
	Phenytoin	Decreased	Increased metabolism
	Valproic acid	Decreased	Same as above
Valproic acid	Carbamazepine	Decreased	?
	Felbamate	Increased	?
	Oxcarbazepine	Decreased	?
	Phenobarbital	Decreased	Increased metabolism
	Phenytoin	Decreased	Same as above
	Primidone	Decreased	Same as above
	Topiramate	Decreased	Same as above
Zonisamide	Carbamazepine	Decreased	Increased metabolism
	Phenobarbital	Decreased	Same as above
	Phenytoin	Decreased	Same as above

*AED = antiepileptic drug.

g. Lamotrigine
i. Mechanism of action: Decreases glutamate and aspartate release, delays repetitive

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firing of neurons, blocks sodium channels.
ii. Rash is a major concern: Lamotrigine must be titrated slowly to avoid a rash.
iii. Valproic acid decreases lamotrigine metabolism: This interaction requires even slower titration and lower final doses.
iv. Also has a FDA indication for maintenance treatment of bipolar I mood disorder.

Table 3. Selected Interactions of Non-antiepileptic Drugs on Antiepileptic Medications

AED*	Other Drug	Effect on the AED	Mechanism
Carbamazepine	Cimetidine Diltiazem Erythromycin Isoniazid Propoxyphene Theophylline Troleandomycin Verapamil	Increased serum conc. Same as above Same as above Same as above Same as above Decreased serum conc. Increased serum conc. Increased serum conc.	Inhibition of carbamazepine metabolism Same as above Same as above Same as above Same as above Increased theophylline metabolism Inhibition of carbamazepine metabolism Inhibition of carbamazepine metabolism
Phenobarbital; primidone	Ethanol	Acute ethanol ingestion may cause CNS additive effects and respiratory depression; chronic ethanol ingestion may result in variable effects	Additive CNS depression and decreased barbiturate metabolism within acute ethanol ingestion
Phenytoin	Anticoagulants, oral	May increase phenytoin serum conc.; decreased/increased anticoagulant effects	Complex mechanism (reference 70)
	Antineoplastics (Bleomycin, Cisplatin, Vinblastine, Methotrexate, Carmustine)	Decreased pharmacologic effect	Unknown, possible decreased absorption due to antineoplastic mucosal damage
	Chloramphenicol	Increased phenytoin serum conc.; decreased/increased chloramphenicol serum conc.	Inhibition of phenytoin metabolism; effect on chloramphenicol unknown
	Cimetidine	Increased serum conc.	Inhibition of phenytoin metabolism
	Diazoxide	Decreased pharmacologic effect; decreased serum conc.	Increased phenytoin metabolism
	Disulfiram	Increased serum conc.	Inhibition of phenytoin metabolism
	Folic acid	Decreased serum conc.	Complex mechanism (Reference 70)
	Isoniazid	Increased serum conc.	Inhibition of phenytoin metabolism
	Phenylbutazone	Increased serum conc.	Inhibition of phenytoin metabolism; plasma protein displacement
	Rifampin	Decreased serum conc.	Increased phenytoin metabolism
	Sulfonamides	Increased serum conc.	Inhibition of phenytoin metabolism
	Trimethoprim	Increased serum conc.	Inhibition of phenytoin metabolism
Topiramate	Hydrochlorothiazide	Increased serum conc.	Unknown
Valproic acid	Meropenem	Decreased serum conc.	Increased valproic acid metabolism
	Rifampin	Decreased serum conc.	Increased valproic acid metabolism
	Salicylates	Increased pharmacologic effect	Plasma protein displacement; increased free valproic conc.

*AED = antiepileptic drug; CNS = central nervous system; conc. = concentration.

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h. Levetiracetam
   i. Mechanism of action: may prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity.
   ii. Pharmacokinetics: not metabolized largely, adjust dose in renal dysfunction, no drug interactions with other antiepileptic drugs.
   iii. Parenteral use: currently indicated by the FDA only for replacement of oral dosing.

Table 4. Pharmacokinetic Parameters of Antiepileptic Medications

Drug	Therapeutic Serum Conc. (mcg/mL)	Bioavailability (%)	Plasma Protein Binding (%)	V_d (L/kg)	Eliminated Unchanged (%)	Clinically Active Metabolite(s)	$t_{1/2}$ (hours)
Acetazolamide	10–14	100	> 90	0.23	100	None	48–96
Carbamazepine	4–12	> 70	40–90	0.8–1.9	Little, if any	10,11-epoxide	8–17
Clonazepam	20–80 ng/mL	100	47–80	3.2	Low percentage	7-amino, low activity	19–50
Ethosuximide	40–100	100	0	0.6–0.7	10–20	None	52–60
Felbamate	Not established	> 90	22–36	0.74–0.85	40–50	None	11–20
Gabapentin	Not established	Dose-dependent	< 3	0.65–1.04	75–80	None	5–7
Lamotrigine	1–13 mcg/mL	98	55	0.9–1.2	10	None	12–55
Levetiracetam	Not established	100	< 10	0.5–0.7	66	None	7
Oxcarbazepine	Not established	100	67	0.7[a]	< 1	10-monohydroxy	9[a]
Phenobarbital	15–40	80–100	40–60	0.7–1	25	None	80–100
Phenytoin	10–20	85–95	> 90	0.6–0.8	< 5	None	~20[b]
Pregabalin	Not established	≥ 90	0	0.5	90	None	6
Primidone	4–12 (20)[c]	90–100	80	0.6	20–40	Phenobarbital PEMA	10–15 17 (PEMA)
Tiagabine	Not established	90–95	96	1.2	—	None	3.2–5.7
Topiramate	Not established	80	13–17	0.6–0.8	70	None	12–21
Valproic acid	40–100 (150)[c]	100	> 90[d]	0.2	< 5	?	8–17
Zonisamide	10–40 mcg/mL	50	40	1.45	35	None	63

[a]MHD = (10-monohydroxy metabolite); PEMA = phenylethylmalonamide.
[b]Michaelis-Menten pharmacokinetics; $T_{1/2}$ varies with serum concentration; therefore, it might be better to express phenytoin elimination in terms of the length of time it takes to clear 50% of the drug from the body, for example.
[c]Upper end of the serum concentration range is not definitely established.
[d]May vary with serum concentration.

i. Oxcarbazepine
   i. Mechanism of action: sodium channel blocker.
   ii. Pharmacokinetics: Active metabolite 10-monohydroxyoxcarbazepine; enzyme inducer, no autoinduction.
   iii. Adverse effects: Hyponatremia more common than with carbamazepine; blood dyscrasias less common than with carbamazepine; 25%–30% of patients with hypersensitivity to carbamazepine will have hypersensitivity to oxcarbazepine; rash.
j. Phenobarbital
   i. Mechanism of action: increases gamma-aminobutyric acid–mediated chloride influx.
   ii. Pharmacokinetics: enzyme inducer.
   iii. Adverse effects: hyperactivity, cognitive impairment.
k. Phenytoin
   i. Mechanism of action: sodium channel blocker.
   ii. Pharmacokinetics: enzyme inducer, nonlinear kinetics.
   iii. Administration considerations
      (a) Intravenous formulation: very basic product. Thus, phlebitis and extravasation

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are concerns; hypotension; maximum infusion rate = 50 mg/minute. Can prepare only in normal saline solution.
(b) Oral suspension: must be shaken well; adheres to feeding tubes and is bound by enteral nutrition products.
iv. Dose-related adverse effects: nystagmus, ataxia, drowsiness, cognitive impairment.
v. Nondose-related adverse effects: gingival hyperplasia, hirsutism, acne, rash, hepatotoxicity, coarsening of facial features.

l. Pregabalin
i. Mechanism of action: unknown.
ii. Pharmacokinetics: not metabolized, renally excreted, reduce dose in renal dysfunction.
iii. Adverse effects: drowsiness, blurred vision, weight gain, edema, angioedema, creatine kinase elevations (three reports of rhabdomyolysis), rash.
iv. Schedule V controlled substance: insomnia, nausea, headache, diarrhea reported after abrupt discontinuation.
v. Dosing: initial dose 150 mg/day divided into 2–3 doses. Increase to maximum of 600 mg/day.
vi. Dosage forms: capsules 25, 50, 75, 100, 150, 200, 225, and 300 mg.
vii. Also has FDA indication for painful diabetic neuropathy, postherpetic neuralgia, and fibromyalgia.

m. Primidone
i. Mechanism of action: increases gamma-aminobutyric–mediated chloride influx.
ii. Metabolized to phenobarbital and phenylethylmalonamide.
iii. Primidone, phenobarbital, and phenylethylmalonamide all have antiepileptic action.
iv. Pharmacokinetics: enzyme inducer.
v. Also used for essential tremor.

n. Tiagabine
i. Mechanism of action: blocks gamma-aminobutyric reuptake in the presynaptic neuron.

o. Topiramate
i. Mechanism of action: blocks sodium channels, enhances gamma-aminobutyric activity, and antagonizes AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)/kainate activity, weak carbonic anhydrase inhibitor.
ii. Pharmacokinetics: not extensively metabolized, eliminated in urine.
iii. Adverse effects: drowsiness, paresthesias, psychomotor slowing (titrate slowly), weight loss, renal stones, acute angle closure glaucoma, metabolic acidosis, and hyperthermia (associated with decreased perspiration—oligohidrosis).
iv. Also has an FDA indication for prophylaxis of migraine headaches.

p. Valproic Acid
i. Mechanism of action: blocks T-type calcium currents, blocks sodium channels, increases gamma-aminobutyric production.
ii. Pharmacokinetics: enzyme inhibitor.
iii. Parenteral use: has FDA indication only for replacement of oral dosing; however, sometimes used for status epilepticus, especially if absence status epilepticus.
iv. Adverse effects: hepatotoxicity, nausea/vomiting, weight gain, interference with platelet aggregation, pancreatitis, alopecia.
v. Also has FDA indications for treatment of mania associated with bipolar disorder and for prophylaxis for migraine headaches.

q. Zonisamide
i. Mechanism of action: sodium channel blocker, blocks T-type calcium currents, weak carbonic anhydrase inhibitor.
ii. Sulfonamide: Avoid in sulfa-sensitive individuals.

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